^2H]-4-[3-[3,6-dihydro-2,5-dimethoxy-3-(1-methylethyl)pyrazin-6-yl]-3-fluoropropyl]-3-(benzyloxycarbonyl)-5-oxazolidinone (**16c**): IR ($CHCl_3$ cast) 2960 (s), 1803 (s), 1718 (s), 1668 (s), 1647 (m), 1416 (s), 1242 (s), 1052 (m), 765 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 5 H, Ph), 5.53-5.22 (AB, 2 H, CbzNCH_2O), 5.21 and 5.20 (AB, 2 H, CH_2Ph), 4.77 (br d, 1 H, $^2J_{HF}$ = 44 Hz, C*H*F), 4.38 (t, 1 H, J = 8 Hz, CbzNC*H*CO), 3.93 (d, 1 H, J = 3.2 Hz, *i*-PrC*H*N), 3.70 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.28 (m, 1 H, MeC*H*Me), 2.23-1.85 (m, 4 H, CH_2CH_2), 1.02 (d, 3 H, J = 7 Hz, CH_3), 0.67 (d, 3 H, J = 7 Hz, CH_3); CI MS (NH_3) 465 (MH^+). Anal. Calcd for $C_{23}H_{29}DN_3O_6F$: C, 59.54; H, 6.52; N, 9.05. Found: C, 59.94; H, 6.61; N, 8.64.

The protected β-fluoroamino acid **16c** (28.1 mg, 60.6 μmol) was hydrolyzed by a procedure analogous to that described above for production of **2a** to afford 7.7 mg (45% yield) of (2*S*,3*R*,6*S*)-[2-^2H]-3-fluoro-2,6-diaminopimelic acid (**2c**): IR (MeOH cast) 3600-2500 (br s), 1725 (m), 1660 (m), 1580 (m), 1498 (s), 1400 (m) cm^{-1}; ^1H NMR (400 MHz, D_2O, DSS) δ 4.88 (d of d, 1 H, $^2J_{HF}$ = 48 Hz, J = 10.4 Hz, C*H*F), 3.85 (t, 1 H, J = 6 Hz, CH_2CHN), 2.10-1.58 (m, 4 H, CH_2CH_2); ^{19}F NMR (376.5 MHz, D_2O) δ -191.69; FAB MS (glycerol) 210 (MH^+).

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Sequential Biocatalytic Kinetic Resolutions

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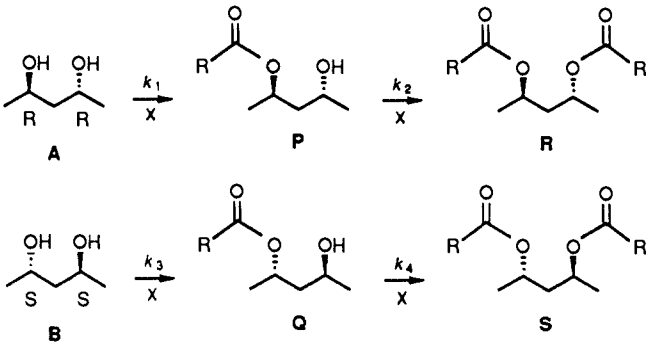
Abstract: Quantitative expressions that govern sequential kinetic resolutions have been developed for calculation of the relative kinetic constants to allow optimization of chemical and optical yields. Enantiomerically pure (2*R*,4*R*)- and (2*S*,4*S*)-2,4-pentanediols have been prepared by biocatalyzed sequential enantioselective esterification in anhydrous isooctane.

The synergistic coupling of an enantioselective reaction with a subsequent kinetic resolution in an asymmetric synthesis leads to a marked enhancement in the enantiomeric purity of the product. In a series of enzymatic studies, it was shown that the initial enantiotopically selective hydrolysis of an achiral diester (asymmetric synthesis) generates optically active monoesters; the same enzyme in turn catalyzes the preferential hydrolysis of the minor antipodal monoester (kinetic resolution). This kinetic pattern is manifested by an increase in the enantiomeric purity of the monoester fraction as the reaction progresses toward completion. This concept has been successfully employed in several enzymic and nonenzymic systems.[1] Similarly, in sequential kinetic resolutions, the second step could likewise improve the enantioselectivity of the first. We had earlier applied this strategy to the preparation of optically active binaphthols.[2] In this paper, we disclose in detail the derivation of the quantitative expressions that govern sequential kinetic resolutions. These equations allow one to define the underlying kinetic parameters that determine the enantiomeric excess (ee) of any chiral species for a given conversion.

Theory

During the enzymatic enantioselective esterification of racemic axially disymmetric diols, two esterification reactions are operating sequentially



where **A** is the fast-reacting enantiomer, (2*R*,4*R*)-(-)-pentanediol, and **B** is the slow-reacting enantiomer, (2*S*,4*S*)-(+)-pentanediol; **P** and **Q** are the corresponding enantiomeric monoesters; **R** and S are the corresponding enantiomeric diesters; **X** is the acyl donor, hexanoic acid; and k_1, k_2, k_3, and k_4 are the four relative second-order rate constants. When the reactions are virtually irreversible and product inhibition is absent in the initial stages, we may write the following:

$$-dA/dt = v_a = k_1[A][\text{acyl-ENZ}] \quad (1)$$

$$-dB/dt = v_b = k_3[B][\text{acyl-ENZ}] \quad (2)$$

$$dR/dt = v_P = k_2[P][\text{acyl-ENZ}] \quad (3)$$

$$dS/dt = v_Q = k_4[Q][\text{acyl-ENZ}] \quad (4)$$

$$dP/dt = v_a - v_P \quad (5)$$

$$dQ/dt = v_b - v_Q \quad (6)$$

Divide (1) by (2) and one obtains

$$dA/dB = k_1[A]/k_3[B] \quad (7)$$

Let

$$E_1 = k_1/k_3 \quad (8)$$

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Integration of (7) gives

$$\ln [[A]/[A_0]]/\ln [[B]/[B_0]] = k_1/k_3 = E_1 \quad (9)$$

Divide (5) by (1) and one obtains

$$-d[P]/d[A] = 1 - v_P/v_A \quad (10)$$

Divide (3) by (1) and one obtains

$$v_P/v_A = k_2[P]/k_1[A] \quad (11)$$

Substituting (11) into (10) yields

$$-d[P]/d[A] = 1 - k_2[P]/k_1[A] \quad (12)$$

Let

$$E_2 = k_2/k_1 \quad (13)$$

$$d[P]/d[A] = E_2[P]/[A] \quad (14)$$

Thus

$$[P] = \frac{[A_0]}{1 - E_2}[([A]/[A_0])^{E_2} - [A]/[A_0]] \quad (15)$$

Similarly

$$[Q] = \frac{[B_0]}{1 - E_3}[([B]/[B_0])^{E_3} - [B]/[B_0]] \quad (16)$$

where

$$E_3 = k_4/k_3 \quad (17)$$

Results

Optically active 2,4-pentanediols have been used extensively as chiral auxiliaries in the asymmetric synthesis of homochiral secondary alcohols.[3] Because these enantiomerically pure axially disymmetric diols are not readily accessible by conventional methods,[4] it was of interest to examine their preparation with sequential enzymatic kinetic resolution. The lipase of *Pseudomonas sp.* (AK) has been successfully used in the resolution of many acyclic alcohols.[5] Hence, several esters of (±)-2,4-pentanediol (**1**) were prepared and exposed to this lipase, and the results are summarized in Table I. The dihexanoyl ester **2** was very slowly hydrolyzed; only a trace of the monohexanoyl ester was detected after several days. The (±)-monohexanoyl ester **3** was hydrolyzed by the enzyme to yield the (2*R*,4*R*)-(−)-diol **1** but with low enantioselectivity ($E = 4$). The (±)-dipropanoyl ester **4** was cleaved to produce the (2*R*,4*R*)-(−)-monopropanoyl ester with an E value of 6. The (±)-diacetyl ester **5** was readily hydrolyzed by the enzyme to yield a mixture of (2*R*,4*R*)-(−)-monoacetyl ester and (2*R*,4*R*)-(−)-diol of low optical purity.

Recently, lipases have been used for the preparative synthesis of macrocyclic lactones via the direct condensation of diacids with diols in nearly anhydrous organic media.[6] Since the enantioselectivity of such biocatalytic macrolactonizations has not previously been examined, it was of interest to conduct an experiment with (±)-**1** as the acyl acceptor. When the lipase AK was incubated with (±)-**1** and hexadecanedioic acid in anhydrous isooctane at 65 °C, a mixture of monolactone (16%, ee = 0.80) and dilactone (6%, ee = 0.23) was formed (Table II). When the products obtained in a parallel experiment are compared with (−)-**1** as the acyl acceptor, it is evident that the enzyme has a *R*-(−) stereochemical preference. Unfortunately, the low chemical and optical yields of the products render this methodology unsuitable for the preparative synthesis of (2*R*,4*R*)- and (2*S*,4*S*)-**1**.

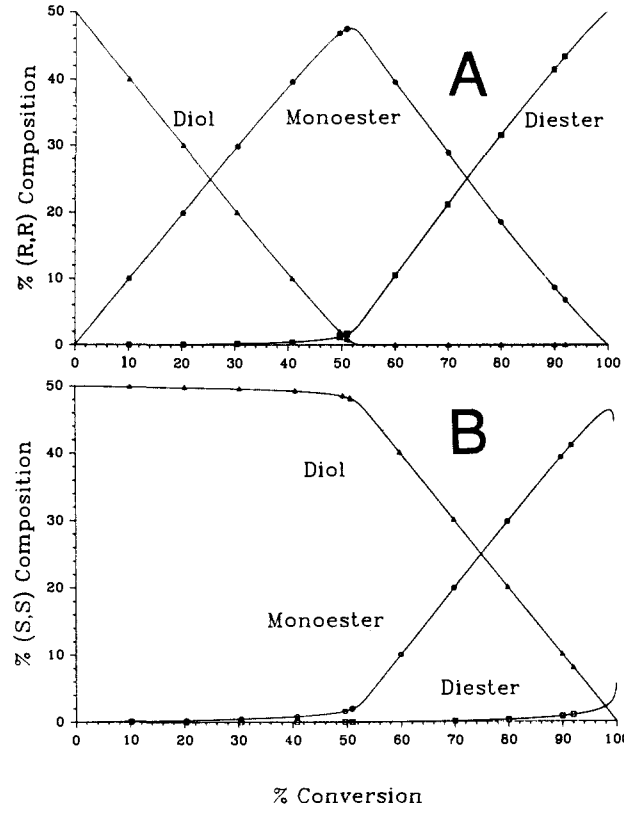

Figure 1. Plot of percent (A) (*R*,*R*) and (B) (*S*,*S*) diester, monoester, and diol as a function of percent conversion [$c = 1 - ([A] + [B])/([A_0] + [B_0])$], where $[A_0]$ and $[B_0]$ denote the initial concentrations of the two enantiomers, A and B. Experimental data: monoester, ●; diester, ■; diol, ▲.

Because the enantioselectivity of lipase-catalyzed esterifications in organic solvents is often higher than the corresponding hydrolytic reactions in water,[5] we turned our attention to examining biocatalytic enantioselective esterifications in nonaqueous media. Thus, (±)-**1** was incubated with the AK lipase in the presence of acyl donors of varying sizes. By terminating the reaction in the early stages, the monoester was isolated and the E value was determined. It is evident that high enantioselectivity was attained only when the acyl donor was greater than C_4 (Table III). However, with the other lipases examined, such as K-10 and PPL, the enantioselectivity of esterification was found to be moderate even when hexanoic acid was used as the acyl donor. The availability of a suitable biocatalytic system allows us to proceed with the theoretical and experimental analyses of sequential resolutions.

The ratios of k_1/k_3 and k_2/k_4 for the AK lipase were found to be 9 and 30, respectively, when propionic acid was used as the acyl donor in isooctane. A marked improvement in enantioselectivity for both steps was observed when hexanoic acid was employed instead; the ratios of k_1/k_3 and k_2/k_4 were found to be 100 and 55, respectively. With use of K-10 lipase and hexanoic acid, the enantioselectivities for the two steps were 12 and 17, respectively (Table IV). The variation in the amount of diester, monoester, and diol with conversion is shown in Figure 1A,B and a plot of enantiomeric excess against conversion is illustrated in Figure 2. The curves were computer-generated with the calculated kinetic constants.

Discussion

Recently, Kaslauskas[2b] described the kinetic treatment of a very specialized case of biocatalytic sequential kinetic resolution by assuming that the enantioselectivity for the two sequential reactions is the same. Because this seldom is the case ($k_1/k_3 \neq k_2/k_4$), it is therefore necessary to introduce the general quantitative expressions to define the kinetic behavior of this type of biocatalytic system. These quantitative expressions allow one to calculate E_1,

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(5) (a) Sih, C. J.; Wu, S. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley Interscience: New York, 1989; Vol. 19, p 63. (b) Chen, C. S.; Sih, C. J. *Angew. Chem.* **1989**, *101*, 711.

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Table I. Lipase AK Catalyzed Enantioselective Hydrolysis of (±)-2,4-Pentanediol Diacyl Esters

compound	stereopreference	incubn time (h)	enantiomeric excess[a] c (%)	ee (S)	ee (P)	E
(±)-2: R = R′ = $C_5H_{11}CO$–	2R,4R	240	22	0.23	0.71	b
(±)-3: R = $C_5H_{11}CO$–, R′ = H	2R,4R	264	47	0.38	0.47	4
(±)-4: R = R′ = C_2H_5CO–	2R,4R	48	29	0.27	0.66	6
(±)-5: R = R′ = CH_3CO–	2R,4R	48	24	0.26	0.75	b

[a] Reaction conditions are described in the Experimental Section. [b] The resulting monoacyl ester was further hydrolyzed to the diol.

Table II. Competitive and Noncompetitive Biocatalytic Macrolactonization of (±)-1 and (−)-1, Respectively

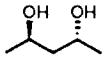
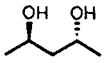
starting diol	incubated time, days	isolated yield, lactones (%)	$[\alpha]_D^{25}$ (deg) (c, $CHCl_3$)
 (−)-1	14	mono (35) di (13)	−29.8 (2.9) −35.9 (1.4)
 (±)-1	5	mono (16) di (6)	−23.8 (1.0) −8.4 (1.0)

Table III. Effect of Acyl Donors on the Enzymatic Enantioselective Esterification of (±)-1

lipase	R	ee_s	ee_P	c	E
Pseudomonas sp. (AK)	$CH_3(CH_2)_8$	0.30	>0.98	0.24	>100
	$CH_3(CH_2)_4$	0.34	>0.98	0.26	>100
	$(CH_3)_2CH$	0.32	0.68	0.32	7
	CH_3CH_2	0.51	0.68	0.43	9
	CH_3	0	0	0.2	1
Pseudomonas sp. (K-10)	$CH_3(CH_2)_4$	0.42	0.77	0.35	12
porcine pancreas lipase (PPL)	$CH_3(CH_2)_4$	0.22	0.72	0.24	8

Table IV. Relative Kinetic Constants for the Biocatalytic Enantioselective Esterification of (±)-1

lipase	R	k_1	k_2	k_3	k_4
AK	CH_3CH_2	9	0.6	1	0.02
	$CH_3(CH_2)_4$	100	1.1	1	0.02
K-10	$CH_3(CH_2)_4$	12	5	1	0.3

E_2, and E_3 (from experimentally determined concentration values of **A**, **B**, **P**, and **Q**), which in turn allow one to generate useful graphs with the computer. The concentration and the enantiomeric excess (ee) of each optically active species at any conversion can then be predicted from the graphs such as Figures 1A,B and 2, respectively. This kinetic overview in turn allows one to maximize the chemical as well as the optical yield of the desired chiral species.

The derivation of the quantitative expressions that govern sequential kinetic resolutions is based on the premise that the reactions are irreversible and that product inhibition is virtually absent. Experimentally, this could often be achieved by the saturation of the reaction medium with the acyl donor ($>10K_m$) or by the use of vinyl or isopropenyl esters[8] as the acyl donor to shift the equilibrium toward the synthetic direction. In the system herein described, we observed that the rate of hydrolyses of the diester and monoester of **1** by the AK lipase was very slow even in aqueous medium (Table I). Thus, we envisaged that by conducting the enantioselective esterification in anhydrous isooctane, reverse catalysis would be negligible. Under these reaction conditions, the minute amount of water that is generated during esterification is insufficient to cause appreciable hydrolysis of the product(s). This supposition was confirmed by the coincidence of the experimental data with the curves (Figures 1A,B and 2) predicted by eqs 15 and 16.

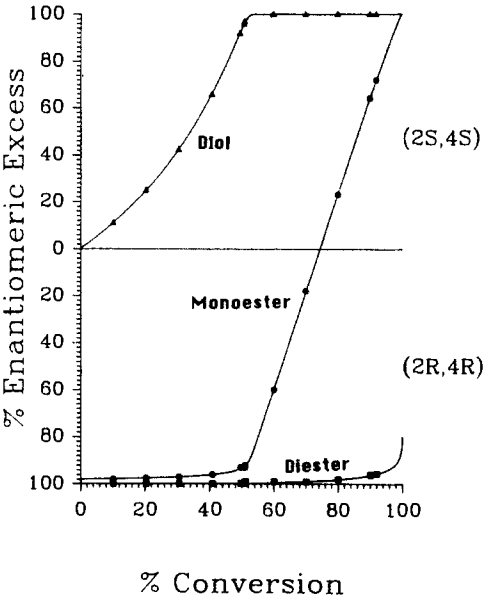


Figure 2. Plot of percent enantiomeric excess of diester, monoester, and diol as a function of percent conversion. The curves were generated with the constants $k_1 = 100$, $k_2 = 1.1$, $k_3 = 1$, and $k_4 = 0.02$. Experimental data: monoester, ●; diester, ■; diol, ▲.

In a preliminary note, we had reported the application of sequential kinetic resolution to the microbial hydrolysis of (±)-binaphthol diacetate. The microorganism *Absidia glauca* has an *S* stereochemical preference for both steps, and the magnitudes of the four relative rate constants were as follows: $k_1 = 12.5$, $k_2 = 205$, $k_3 = 1$, and $k_4 = 3.7$. In this system, the rate constants of the second parallel steps are greater than those of the first. That is, $k_2 > k_1$ and $k_4 > k_3$. On the other hand, in the sequential enantioselective acylation of **1** in isooctane, the first esterification reaction rate is considerably faster than the second; the relative rate constants for hexanoic acid as the acyl donor were $k_1 = 100$, $k_2 = 1.1$, $k_3 = 1$, and $k_4 = 0.02$. Although these two types of sequential reactions are mediated by different biocatalytic systems, such kinetic behavior can be explained from steric consideration of the substrates during catalytic turnover and can be modeled equally well by the derived expressions.

As shown in Table IV, the enantioselectivity of lipase-catalyzed esterification depends critically on the size of the acyl donors, which is in accord with the results described by Sonnet.[7] Although this phenomenon has not been systematically studied, the longer chain acyl donors such as hexanoic or decanoic acid appear to be more enantioselective than the shorter chain acyl donors.[4]

Although the quantitative expressions herein described have been applied only to axially disymmetric diols, they can be broadly used for the kinetic analysis of other types of coupled enantioselective systems, for example, the enantioselective hydrolysis of

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a monoester and the subsequent enantioselective esterification of the chiral alcohol with a different acyl donor[10] in a suitable organic solvent, saturated with water.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker WM-200 spectrometer in deuteriochloroform with tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin-Elmer Model 241C polarimeter in the indicated solvents. A Model M-6000 pump equipped with a U6K injector and a Model 77 double-beam UV (254-nm) detector (Waters Associates) were used for high-pressure liquid chromatography (HPLC). Thin-layer chromatography (TLC) was performed on plastic sheets coated with 0.25-mm thickness of silica gel 60F-254 (Macherey-Nagel, Germany). Flash column chromatography was performed with Baker silica gel (40 μm). All solvents were glass-distilled prior to use. Gas chromatography (GC) was performed with a Varian aerograph Model 2400 instrument. All other chemicals and solvents of the highest quality grade available were purchased from Aldrich Chemical Co. or Sigma Chemical Co. Pirkle Type 1-A column (D-phenylglycine, 4.6 mm × 25 cm) was a product of Regis Chemical Co. Lipases AK and K-10 (*Pseudomonas sp.*) were purchased from Amano; porcine pancreatic lipase (PPL) was a product of Sigma.

(±)-2,4-Pentanediol (1). 2,4-Pentanediol, purchased from Aldrich, consisted of a mixture of isomers. The mixture (10 g) was dissolved in 100 mL of diethyl ether, and the solution was kept at −30 °C for 5 days. The (±)-**1** crystallized as a white solid, whereas the *meso*-diol remained in the ethereal solution. After the solid was filtered and washed with cold ether, the desired (±)-**1** (4 g) was collected.

Enzymatic Hydrolysis of (±)-2. The reaction mixture contained 500 mg of (±)-**2** and 500 mg of AK lipase in 5.0 mL of 0.2 M phosphate buffer (pH 8.0). The mixture was incubated on a rotary shaker (200 rpm) at 33 °C, and the process of the reaction was followed by TLC analysis. After 10 days, the reaction was terminated, and the reaction mixture was extracted with ethyl acetate (three times, 15 mL each). The combined organic layer was dried over sodium sulfate and concentrated to dryness. The residue was chromatographed over a silica gel column, and the column was successively eluted with the following: (a) hexane/ethyl acetate (3:1) to obtain 439 mg of the residual (+)-**2**, $[\alpha]^{23}_D$ +8.6° (*c* 2.9, $CHCl_3$) (ee = 0.23); (b) hexane/ethyl acetate (2:1) to yield 57 mg of (−)-monohexanyl ester, $[\alpha]^{23}_D$ −15.4° (*c* 2.9, $CHCl_3$) (ee = 0.71); (c) ethyl acetate to afford 8 mg of (−)-diol, $[\alpha]^{23}_D$ −36.4° (*c* 0.8, $CHCl_3$) (ee = 0.98). The estimated molar ratio of diester to monoester to diol (**2**:**3**:**1**) was 5.2:1:0.5, and the percent conversion was estimated to be around 22%.

Enantioselective Hydrolysis of (±)-3 by AK Lipase. A suspension of 300 mg of (±)-**3** and 150 mg of AK lipase in 2 mL of 0.2M phosphate buffer (pH 8.0) was vigorously stirred at 25 °C. After 11 days, the reaction mixture was extracted with ethyl acetate and the residue was chromatographed over a silica gel column. Elution of the column with the same solvent system as before gave 157 mg of remaining (+)-**3**, $[\alpha]^{23}_D$ +9.7° (*c* 0.9, $CHCl_3$) (ee_S = 0.38), and 140 mg of diol, $[\alpha]^{23}_D$ −16° (*c* 0.7, $CHCl_3$) (ee_P = 0.43). Conversion was estimated to be 47%, and E = 3.6.

AK Lipase Catalyzed Hydrolysis of (±)-4. To 200 mg of (±)-**4**, suspended in 2 mL of 0.2 M phosphate buffer (pH 8.0), was added 200 mg of AK lipase. The contents were vigorously stirred at 25 °C for 48 h. Following the same workup and chromatographic procedures as before, 140 mg of (+)-**4** (ee = 0.27) and 55 mg of (−)-monopropanoyl ester were obtained. Conversion was 29%, and E = 6.

Biocatalytic Macrocyclic Lactonization of (+)-1. The reaction mixture contained hexadecanedioic acid (4 mmol, 1.15 g), (±)-**1** (41 nmol, 417 mg), and AK lipase (8 g) in 400 mL of anhydrous isooctane. The contents were incubated on a rotary shaker (200 rpm) at 65 °C for 5 days. The mixture was filtered to remove the protein powder, and the protein was exhaustively washed with ethyl acetate. The combined organic solvent was concentrated to dryness in vacuo. The residue was chromatographed over a silica gel column (2.2 × 40 cm), and the column was eluted with a solvent mixture consisting of hexane/ethyl acetate (30:1 to 20:1 for the first 40 fractions; 3:1 for fractions 41–68; and finally 3:1 ethyl acetate/methanol to elute the remaining diol). Fractions 4–6 were combined and concentrated to dryness to yield 232 mg of an oily monolactone, $[\alpha]^{23}_D$ −23.8° (*c* 1.0, $CHCl_3$). Fractions 10–15 gave 90 mg of a solid dilactone, $[\alpha]_D$ −8.4° (*c* 1.0, $CHCl_3$). Fractions 69–72 contained 89 mg of (+)-**1**, $[\alpha]^{23}_D$ +15.3° (*c* 1.8, $CHCl_3$).

Enzymatic Condensation of (2*R*,4*R*)-2,4-Pentanediol ((−)-1) with Hexadecanedioic Acid. To a suspension consisting of hexadecanedioic acid (2 mmol, 573 mg) and (2*R*,4*R*)-(−)-**1** (2 mmol, 208 mg) in 200 mL of anhydrous isooctane was added 4 g of AK lipase. The mixture was incubated on a rotary shaker (200 rpm) at 65 °C for 14 days. The reaction mixture was worked up as previously described for the corresponding racemic diol experiment to yield 245 mg of an oily monolactone, $[\alpha]^{23}_D$ −29.8° (*c* 2.9, $CHCl_3$), and 92 mg of dilactone, $[\alpha]^{23}_D$ −35.9° (*c* 1.4, $CHCl_3$).

Enantioselective Esterification of (±)-1 Catalyzed by AK Lipase. To a suspension of hexanoic acid (8 mmol, 930 mg) and (±)-2,4-pentanediol (**1**) (4 mmol, 417 mg) in 80 mL of anhydrous isooctane was added 1 g of lipase AK. The reaction mixture was incubated on an incubator rotary shaker (2-in. stroke, 200 rpm) at 65 °C. Samples were taken at 7, 16, 23, 37, 48, 62, 88, and 240 h.

Quantitative Determination of the Diester, Monoester, and Diol. Each sample was saturated with NaCl and then extracted with ethyl acetate (three 5-mL portions). After being dried over sodium sulfate, the organic extract was evaporated to dryness in vacuo. An aliquot of each sample was quantitatively analyzed by gas–liquid chromatography with a 5-ft Chromosorb WHP column with 5% OV-101 as the stationary phase. The flow rate was 30 mL/min. The initial column temperature was 60 °C and was gradually increased at a rate of 10 °C/min until the final temperature of 100 °C was reached. The retention times were 2.5 min for the diol, 4 min for the monoester, and 6.5 min for the diester. A standard solution of the diol, monoester, and diester was preanalyzed under the same conditions. The ratio of integral peak areas for equal molar concentrations of diol to monoester to diester was 0.32:1:1.8.

Determination of the Enantiomeric Excess of the Diester, the Monoester, and the Diol Fractions. The diester, monoester, and diol were readily separated on a silica gel column (1 × 15 cm). The column was first eluted with a solvent mixture consisting of hexane/ethyl acetate (3:1) to obtain the diester, the monoester was eluted off the column with hexane/ethyl acetate (2:1), and the diol was eluted off the column with ethyl acetate. The diol and the monoester were treated with (+)-2-methoxy-2-(trifluoromethyl)phenylacetyl (MTPA) chloride to form their respective (+)-MTPA derivatives. The diester was hydrolyzed to the diol with 1 N NaOH and was then converted into the (+)-MTPA derivatives. The (+)-MTPA derivatives were analyzed with a Pirkle chiral column (4 mm × 25 cm) with hexane/ether (25:1) as the mobile phase. The flow rate was 0.8 mL/min, and the absorbance at 254 nm was monitored with a UV detector. The retention times of these (+)-MTPA derivatives were 12 min for the *R*,*R* monoester, 13.4 min for the *S*,*S* monoester, 14 min for the *R*,*R* diester, and 16 min for the *S*,*S* diester.

Calculations. E_1, E_2, and E_3 can be calculated from the experimentally determined concentration values of **A**, **B**, **P**, and **Q** with eqs 9, 15, and 16. The four relative rate constants (k_1, k_2, k_3, k_4) can then be obtained from eqs 8, 13, and 17 assuming $k_3 = 1$. In these experiments, four sets of data were determined for each point and the concentrations of **A**, **B**, **P**, **Q**, **R**, and **S** were expressed in percentages as follows:

$$[A_0] = [A] + [P] + [R] = 50\% \tag{18}$$

$$[B_0] = [B] + [Q] + [S] = 50\% \tag{19}$$

ee_1, ee_2, and ee_3 are the enantiomeric excess (ee) of the remaining diol, monoester, and diester, respectively.

$$ee_1 = \frac{[B] - [A]}{[B] + [A]} \tag{20}$$

$$ee_2 = \frac{[P] - [Q]}{[P] + [Q]} \quad \text{when } [P] > [Q] \tag{21}$$

or

$$ee_2 = \frac{[Q] - [P]}{[Q] + [P]} \quad \text{when } [P] < [Q] \tag{22}$$

$$ee_3 = \frac{[R] - [S]}{[R] + [S]} \tag{23}$$

For each point, concentrations of **A**, **B**, **P**, **Q**, **R**, and **S** were calculated from the experimental data; ([P] + [Q]), ([R] + [S]), ee_1, ee_2, and ee_3 were calculated with eqs 18–23. E = 100 was used when it was greater than 100. The solid curves in Figures 1A,B and 2 were computer-generated with E_1 = 100, E_2 = 0.011, and E_3 = 0.02, which were calculated from eqs 9 and 15–23. Conversion, c, was defined as

$$c = 1 - \frac{[A] + [B]}{[A_0] + [B_0]} \tag{24}$$

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(10) Roberts, S. M. Personal communication.